MORPHOLOGICAL CHANGES IN THE FOWL FOLLOWING CHRONIC OVERDOSAGE WITH VARIOUS STEROIDS

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THREE PLATES (FOURTEEN FIGURES)

In comparison with the mammals, the fowl offers some definite advantages as a test object for certain physiological studies. A pure breed is comparatively easy to obtain in large numbers hatched on the same day and treatment can be started during the first few days of life since the newly-hatched chick is quite resistant to repeated daily injections. Furthermore, the avian subject is particularly sensitive to certain experimental conditions to which mammals are relatively resistant. Thus, the entire development of our knowledge concerning the physiology of vitamins is largely due to the fact that the bird is especially sensitive to vitamin B_1 deficiency and hence served as an excellent test object for the study of the first vitamin to be subjected to systematic experimental investigation. In connection with endocrine research the pigeon's crop and the capon's comb, as sensitive indicators of lactagogue and testoid activity, proved of outstanding value. Our earlier investigations have shown that young chicks are also especially sensitive to the toxic actions of certain steroids (Selye, '42; Selye and Stone, '43). In view of these considerations it appeared of interest to undertake a systematic study of the changes induced by various steroids following chronic administration of large doses throughout the period of active growth and development.

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For this purpose a group of 144 2-day-old, single-combed white Leghorn chicks were used. They were sub-divided into twelve groups, each consisting of twelve chicks. Although it is difficult to determine with certainty the sex of newly-hatched white Leghorns, autopsy at the end of the experiment revealed that in most instances the number of males and females was approximately the same in each group. The average weight of the birds at the onset of the experiment was 40–45 gm. One group of twelve chicks served as untreated controls, while each of the other groups was treated with a different steroid compound. The steroids were administered subcutaneously in a dose of 0.5 mg. in 0.05 cc. of peanut oil twice daily during the first 20 days. This dose was gradually raised as the chicks grew in size. Bidaily injections of 1 mg. in 0.1 cc. of oil were given for the next 15 days, 2 mg. during the following fortnight and after that 4 mg. until the termination of the experiment. The amount of oil used as vehicle for the steroids never exceeded 0.1 cc. per injection in order to prevent the formation of oil pouches. Not all steroids were soluble in such small amounts of oil, but the more insoluble ones were given as crystal suspensions. Thus the total daily dose finally reached 8 mg. in 0.2 cc. of oil. Only in the case of the highly potent estradiol did we deviate from this standard dosage inasmuch as we administered 1 γ of this compound instead of 1 mg. of any of the other steroids. The speed with which the initial dose was raised and the amount of oil given per day were the same, however, in the estradiol and in the other groups.

Four birds of each group were killed on the twentieth, four on the forty-fifth and four on the ninety-fifth day of the experiment in all groups, excepting the last four birds of the series treated wtih acetoxy-pregnenolone which had to be killed on the seventieth day because we did not have sufficient quantities of this compound to proceed longer. At each of these three dates the organs of the birds were fixed in "Susa" mixture immediately after the animals were killed by bleeding. After fixation the organs which were of particular

TABLE 1

Morphological changes in the fowl following overdosage with various steroids.

STEROID	DAYS OF TREATMENT	BODY WEIGHT	KIDNEY	HEART	LIVER	SPLEEN	PANCREAS	ADRENAL	THYROID	TESTIS	OVARY	COMB	UROPYGIAL	BURSA
Controls	20	128	1.229	1.017	3.271	0.104	0.718	0.018	0.005	0.022	0.030	0.052	0.088	0.391
	45	454	4.110	2.483	9.646	0.574	1.698	0.051	0.023	0.097	0.088	1.373	0.529	1.895
	95	1162	11.036	6.484	27.355	2.213	3.824	0.130	0.101	0.335	0.246	4.062	0.691	3.165
Cholesterol	20	115	1.433	0.752	2.883	0.105	0.698	0.022	0.007	0.032	0.028	0.093	0.098	0.421
17-iso-octyl-Δ^5-androstene-	45	376	4.026	2.086	9.064	0.452	1.657	0.038	0.025	0.042	0.132	0.239	0.481	1.870
3(β)-ol, M.P. 149°C.	95	1120	8.242	5.253	20.406	2.283	3.445	0.101	0.093	0.415	0.287	8.926	0.670	3.675
α-Estradiol	20	135	1.676	0.933	3.257	0.141	0.873	0.023	0.008	0.028	0.025	0.064	0.130	0.608
$\Delta^{1,3,5}$-estratriene-3, 17-	45	440	4.479	1.731	10.286	0.624	1.703	0.048	0.044	0.046	....	0.515	0.619	1.646
(α)-diol, M.P. 176–177°C.	95	1183	10.028	5.377	23.556	2.003	3.068	0.104	0.123	0.640	0.252	6.166	0.775	4.547
Androstenedione	20	115	1.208	0.805	2.447	0.089	0.547	0.019	0.010	0.017	....	1.348	0.057	0.315
Δ^4-androstene-3, 17-dione	45	375	3.907	2.231	8.174	0.449	1.463	0.039	0.032	0.052	0.077	6.499	0.407	0.738
M.P. 169–171°C.	95	1001	7.101	4.671	18.804	1.292	2.671	0.087	0.076	0.259	0.159	11.523	0.692	0.499
Androstenediol	20	123	1.372	0.816	2.832	0.099	0.729	0.026	0.007	0.011	0.021	0.823	0.086	0.410
Δ^5-androstene-3(β), 17(α)-	45	421	3.942	2.258	8.984	0.542	1.616	0.048	0.034	0.048	0.079	6.236	0.605	1.669
diol, M.P. 182–183°C.	95	1043	8.063	4.622	19.553	1.614	2.827	0.087	0.064	0.126	0.203	16.871	0.821	0.352
Dehydro-Iso-Androsterone	20	108	1.507	0.836	2.609	0.080	0.611	0.022	0.010	0.020	0.015	0.813	0.046	0.313
Δ^5-androstene-3(β)-ol-	45	456	4.316	2.258	10.268	0.691	1.718	0.046	0.026	....	0.086	4.198	0.498	1.783
17-one, M.P. 146°C.	95	1008	8.157	4.202	21.218	1.991	2.700	0.089	0.083	0.533	0.190	7.281	0.570	1.388
Methyl-Testosterone	20	96	0.895	0.888	1.962	0.041	0.431	0.016	0.006	0.017	0.013	0.735	0.030	0.078
17-methyl-Δ^4-androstene-	45	370	3.150	1.880	7.270	0.306	1.127	0.035	0.013	....	0.083	6.645	0.294	0.176
3-one-17-ol, M.P. 163–164°C.	95	875	7.724	4.248	18.419	1.431	2.165	0.063	0.064	0.509	0.189	9.101	0.795	0.096
Progesterone	20	126	1.573	0.939	3.270	0.100	0.708	0.021	0.012	0.027	0.021	0.093	0.116	0.502
17-ethyl-Δ^4-androstene-	45	478	4.365	2.556	11.587	0.614	1.513	0.034	0.022	0.051	0.079	0.580	0.707	1.782
3, 20-dione, M.P. 128°C.	95	1134	8.636	5.867	22.647	1.693	2.637	0.072	0.076	1.090	0.214	2.837	0.759	2.522
Desoxycorticosterone Acetate														
17-ethyl-Δ^4-androstene-3,	20	128	2.206	1.637	4.722	0.096	0.828	0.023	0.009	0.087	0.031	0.091	0.106	0.494
20-dione-21-ol acetate,	45	358	4.657	3.482	11.487	0.238	1.228	0.042	0.015	0.049	0.114	0.308	0.258	1.692
M.P. 152°C.	95	1050	14.352	7.606	23.377	0.765	2.403	0.049	0.042	0.201	....	1.941	0.611	1.277
Pregnenolone	20	125	1.516	0.912	3.116	0.112	0.701	0.022	0.008	0.034	0.023	0.117	0.074	0.507
17-ethyl-androstene-3(β)-ol-	45	633	4.657	2.373	10.033	0.606	1.872	0.053	0.028	0.081	0.109	1.259	0.597	2.558
20-one, M.P. 186°C.	95	1288	8.763	5.175	24.403	2.201	3.200	0.093	0.090	0.417	0.277	6.938	0.851	4.697
Acetoxy-Pregnenolone														
17-ethyl-Δ^5-androstene-3(β),	20	130	1.511	0.935	3.012	0.136	0.683	0.019	0.009	0.043	0.022	0.115	0.083	0.639
21-diol-20-one acetate,	45	433	4.713	2.353	8.814	0.620	1.641	0.047	0.031	....	0.111	0.384	0.604	2.861
M.P. 183–184°C.	70	840	6.355	3.816	18.582	1.519	2.487	0.069	0.062	0.220	0.171	3.054	0.740	4.870
Ethinyl-Testosterone	20	119	1.294	0.842	2.915	0.122	0.576	0.017	0.006	0.021	0.021	0.084	0.103	0.662
17-ethinyl-Δ^4-androstene-3-	45	385	3.988	2.046	8.545	0.549	1.340	0.045	0.032	0.075	0.077	3.301	0.635	1.789
one-17(α)-ol	95	1001	7.571	4.897	18.852	1.540	2.353	0.092	0.069	1.747	0.179	5.863	0.971	3.723

[1] Due to an error these organs have not been weighed.

interest to us were weighed on an analytical balance and subsequently sectioned for histological study. Table 1 summarizes the mean organ weights in grams. Each group usually consisted of the same number of cockerels and pullets and essentially the organs of the males and females responded in the same manner to the steroids given. Hence only average weights are recorded without separating the sexes except in the case of the gonads. In perusing the table it must be kept in mind that owing to the difficulty of obtaining many of the steroids in sufficiently large quantities it was not possible to have more than four birds in each of the three groups treated with the same steroid. Hence, the means given in the table are not suitable for statistical analysis and, unless the deviat from the mean organ weight of the controls is extremely striking, it is not justifiable to speak of atrophy or hypertrophy on the basis of the organ weights, except if the histological appearance of the tissues gives definite evidence of such changes. It will also be kept in mind that since cholesterol is not absorbed from the subcutaneous tissues and exerts no pharmacological actions when administered by tl , route, the birds treated with cholesterol give us a second set of normal reference values differing from those marked "controls" only in that they were subjected to the same bidaily handling and injecting which was unavoidable in the animals treated with the other steroids. Since estradiol was given at a lower dose range than the other steroids and the last group of the acetoxy-pregnenolone series was treated for 70 days only, these groups are not directly comparable with those of the other compounds. It will also be noted that the common popular names of the steroids are given in block letters but the full systematic names (for terminology see Selye, '42a) and the melting points of the samples used are likewise mentioned. This will help to identify the compounds and to give an approximate idea of the degree of purity of the preparations employed in this work.

Perusal of the table indicates that the body weight increase was not very significantly influenced by any of the steroids

although methyl-testosterone caused some inhibition of development.

The kidneys showed a very definite increase in size after desoxycorticosterone (D.C.A.) administration and their surface became extremely irregular (figs. 1 and 2). This was particularly obvious in the 20- and 45-day groups. Histological examination revealed changes similar to those described in the earlier acute experiments (Seyle, '42; Selye and Stone, '43). However, the tubular hypertrophy was not as marked and the glomerular changes were more severe in these chronic experiments and indeed glomerular sclerosis and hyalinization of the tuft capillaries became more and more pronounced as the experiment went on. The individual glomeruli were greatly enlarged and the walls of the capillaries thickened. In many instances epithelial crescents appeared in the parietal wall of Bowman's capsule and, in the final stages, the renal corpuscles were transformed into a scar-like mass. Many of the tubules were obliterated by more or less basophilic hyaline casts and the stroma between the tubules and glomeruli was heavily infiltrated in certain circumscribed areas by leukocytes among which eosinophiles were often prominent. The arteries — and to a lesser degree the veins — of the kidney showed a pronounced thickening of their walls and foci of degeneration were not infrequent especially in the small arterial vessels. It is noteworthy that the vessels in other organs showed no comparable degree of thickening. Qualitatively similar changes were also detectable in the kidneys of progesterone and acetoxy-pregnenolone treated chicks although the total size of the organ was not above normal. However, the degree of nephroscelerosis was by far the greatest after D.C.A. administration, and more pronounced following progesterone than after acetoxypregnenolone treatment (figs. 3–8). It is noteworthy that the testoid compounds, which are most active among all the steroids in causing renal enlargement in mammals (Selye, '41), are completely devoid of this effect in the bird. Indeed, the most potent testoids of

our series (androstenedione, methyl-testosterone and ethinyl-testosterone) elicited a decrease in renal size.

The heart shows a definite increase in size in all groups treated with D.C.A. This increase is not merely due to a greater blood content resulting from cardiac dilatation, since the hearts were weighed after removing the blood. Histologically the cardiac muscle fibers themselves — especially those of the left ventricle — proved to be hypertrophied and it appears logical to regard the change as a compensatory hypertrophy secondary to the renal changes just as it occurs in human cases of Bright's disease. The other steroids did not cause any significant cardiac hypertrophy, with the possible exception of progesterone whose effect could be explained on the same basis.

The liver was definitely enlarged in the early stages of D.C.A. overdosage as shown by the 20-day group. At 45 days this enlargement was pronounced and at 95 days it was no longer evident. In this case the other steroids were again comparatively inert with the exception of methyl-testosterone which, at least in the early stages, appeared to exert an inverse effect causing a decrease in the size of the liver reminiscent of the decrease in kidney size elicited by this compound.

The spleen was definitely atrophic in the D.C.A. treated group and slightly subnormal in its development in the birds treated with most of the other steroids. This effect is essentially similar to that observed in mammals, in which it was found that severe overdosage with all hormonally active steroids causes some degree of splenic involution.

The pancreas showed no definite changes in size or histological structure, but in the D.C.A. treated group during the early stages of treatment edema of the pancreas was of frequent occurrence. This result is not surprising, since, probably as a result of the renal changes and the subsequent derangement in water metabolism, tissue edema and fluid accumulations in the serous cavities were invariably detectable in the D.C.A. treated birds. This edema tendency was much less pronounced in the progesterone and acetoxy-

pregnenolone treated chicks and not demonstrable in those receiving other steroids.

The adrenals were markedly atrophic in the D.C.A. treated group and exhibited signs of mild atrophy in the birds treated with progesterone, acetoxy-pregnenolone and methyl-testosterone. Histologically this atrophy was particularly obvious in the cortical cells, while the medullary elements appeared to be practically normal. In the bird, at least at the dose levels tested in this experiment, D.C.A. failed to elicit the medullary atrophy which it produces in mammals following chronic administration of large amounts (Selye, '40; Selye and Hall, '43). The fact that progesterone and methyl-testosterone also produce a certain degree of cortical atrophy is in agreement with previous observations in the rat (Selye, '40).

The thyroids showed mild stimulation — as judged both by their weight and by their histological appearance — under the influence of the small amounts of estradiol administered in this series, while D.C.A. caused definite involution, especially in the chronically treated animals of the second and third group.

The testes revealed an accelerated development in the last group of the progesterone and ethinyl-testosterone treated birds. This could be confirmed both by weight and by histological signs of maturation. It is peculiar that this effect was limited to the two most active luteoid compounds of our series, but before accepting definitely that these observations are significant they would have to be repeated on a larger number of animals. After 20 days of treatment, both in the D.C.A. and to a lesser degree in the progesterone group, some of the testes were enormously enlarged due to fluid accumulation in the spermatogenic tubules. In these cases the greatly distended tubules were lined by a simple cuboidal or squamous epithelium and showed no signs of spermatogenic activity (figs. 7, 9 and 10). It is difficult to understand why the matrix of the spermatogenic epithelium should assume such a specific fluid secreting function under the conditions of our experiment. However, these changes were only seen

in those males of the D.C.A. and progesterone group which exhibited the greatest degree of tissue edema and fluid retention in the serous cavities. Hence, it appears reasonable to assume that the fluid accumulation in the testicular tubules is only a special manifestation of the general edema tendency. Curiously, the stroma of the testes did not partake in this edema. Since these gigantically enlarged testes were eliminated from our averages the mean weight of the male gonads is not particularly augmented as judged by the table. In the 45- and 95-day series this peculiar testis change was never observed, presumably because by that time the generalized edema tendency of the tissues had subsided. The Leydig cells revealed varying degrees of atrophy with all hormonally active steroids, a fact which confirms previous observations on rats (Selye and Albert, '42).

The ovaries showed no striking histological changes in any of the groups, except in the 20-day D.C.A. group in which stroma edema and enormous cystic dilatation of some follicles was evident in a certain number of cases (fig. 8). This response is probably equivalent to the testicular enlargement in the males.

The comb development in the birds of this series (which were not castrates) depends, of course, both upon the internal secretion of their testes and upon the testoid activity of the various compounds with which they were treated. Since during the first 20 days of the experiment the gonads were still very immature and produced no significant amounts of comb growth stimulating substances, any increase in comb size observed during this period can be ascribed to the action of the injected steroids. There was no very significant difference in the responsiveness of the comb of the two sexes at this age. Perusal of the table and histological examination of the degree of mucoid connective tissue formation in the combs, indicates that androstenedione proved more potent than methyl-testosterone in inducing comb-growth during the first 20 days. This is contrary to expectations, since previous investigators (Tschopp, '35; Ruzicka et al, '35; Ruzicka and

Wettstein, '35; Deanesly and Parkes, '36; Korenchvesky et al., '37; Kochakian, '38) claimed that, both in the fowl and in the rat test, androstenedione is definitely less active than testosterone, which in turn is known to be less active than methyl-testosterone. In our experiment androstenedione proved much more active than any of the other steroids tested. The combs of the chicks treated with androstenedione became so large and heavy that they hung down over the side of the head at a time when the combs of the methyl-testosterone chicks were comparatively slightly enlarged and still erect. The main difference between our experimental arrangement and that used by other investgators is that we employed much larger doses and it is quite possible that methyl-testosterone would compare more favorably with androstenedione at low dose levels. It will also be noted that at the twentieth day, before endogenous testoid production could interfere with the test, androstenediol and dehydro-iso-androsterone also caused significant comb growth while no definite enlargement was induced by progesterone, pregnenolone, acetoxy-pregnenolone or ethinyl-testosterone, although the birds received 1 mg. a day for 20 days by this time. This confirms our previous observations concerning the lack of testoid activity in progesterone, D.C.A., pregnenolone and acetoxy-pregnenolone (Selye and Albert, '42; '42a; Albert and Selye, '42). The only surprising fact is that while in the rat ethinyl-testosterone is quite active in stimulating both the seminal vesicles and the prostate — as judged by our above-mentioned observations — in the bird it proves unusually inactive. This result is in agreement with the findings of Inhoffen et al. ('38) who report a negative capon comb test with 2 mg., although Emmens and Parkes ('39) stated that when given by mouth the compound is about one sixth as comb-growth-stimulating as androsterone. In ovariectomized women Salmon and Geist ('40) noted no testoid effects following treatment with ethinyl-testosterone. It is not impossible, however, that the inactivity of the compound in the chick is partly due to lack of efficient absorption from the subcutaneous tissue since the compound is extremely

insoluble. It is also noteworthy that after 45 days of treatment both pregnenolone and ethinyl-testosterone appeared to cause some comb growth but since at about this time the testoid secretion of the gonads begins to come into play, care must be exercised in interpreting these results. At 95 days, however, all compounds, except androstenediol, but including the highly testoid androstenedione and methyl-testosterone, actually inhibited comb growth or at least failed to stimulate it in comparison with controls of the same age. This is probably due to the fact that all testoids cause compensatory atrophy of the Leydig cells and thus inhibit endogenous testoid production (Selye and Albert, '42). Since 8 mg./day of the testoid compounds were given during the last 50 days of the experiment it appears reasonable to assume that the normal testis produces daily at least the equivalent of the testoid potency represented by this amount.

The uropygial gland of the fowl is situated on the dorsal side of the last tail vertebrae and produces a secretion which helps to keep the feathers covered by an oily layer. It is well developed in males and females. Histologically it resembles the sebaceous glands of the mammals and more particularly the large preputial glands of the rodents. Like the latter, it develops in the shape of two separate glands whose ducts end in the genital region. It is known that after extirpation of the uropygial glands the plumage of the birds becomes dry and brittle. Certain abnormalities in skeletal development may also appear, but it is questionable whether the latter may be regarded as specific or whether they are merely due to the general damaging effect of the inadequacy of plumage development (Hou, '28; '28; Guareschi, '34; Murphy, '36). Curiously there appears to be no literature concerning hormonal influences regulating the development and function of this typical gland of the birds, although it is known that during the mating season it produces an increased amount of secretion at least in certain avian species. While the preputial glands enlarge under the influence of testoid compounds (Selye and Albert, '42; '42a; Albert and

Selye, '42), our observations show that the reverse is true of the uropygial glands in birds, at least during the first 20–45 days of experiment. After that, apparently some degree of adaptation occurs and the gland resumes its normal size and histological appearance in spite of continued treatment. Since this gland functions by means of holocrine secretion it is rather difficult to establish whether the testoids decrease the number of cells which develop in the gland, or whether they increase the number lost through excretion. Should the glands decrease in size because of an increased excretion of the cells which make up their parenchyme the difference between bird and mammals would not be a fundamental one.

The bursa Fabricii (for literature see Boyden, '22) is a lympho-epithelial organ attached in a tonsil, or appendix-like manner, to the anal end of the alimentary canal of the fowl. Extirpation of this organ does not elicit any detectable deficiency symptoms (Riddle and Tange, '28; Riddle and Krizenecky, '33). However, like the thymus of mammals — to which the bursa has often been compared — it is very sensitive to most, if not all, hormonally active steroids. It underwent particularly marked involution in the testosterone-treated birds of this series in which after 45 days of treatment all the lymphatic elements of the bursa have completely disappeared and only the stroma and the epithelial lining of the crypts remained (figs. 11 and 12). As in the case of the uropygial glands, a certain degree of adaptation appears to occur in the case of long continued treatment since some of the lymphatic elements re-appear in the bursae of the animals treated for 95 days.

The development of fat tissue was greatly increased in the birds chronically treated with D.C.A. This was all the more remarkable, since they were actually smaller than most of the other birds and they maintained an approximately normal weight, only because of the large fat accumulations. The fat depositions were most pronounced in the subcutaneous tissue, the vicinity of the pericardium, the omentum and around the kidneys (figs. 1 and 2). Zondek ('41) described

marked hyperlipemia and fatty degeneration of various organs in cocks chronically treated with folliculoid compounds, but in our estradiol experiments adiposity did not develop.

The estradiol experiment, summarized in the table, was performed on a comparatively very low dose level, since our previous experiments in the rat indicated that mammals are extremely sensitive to such minute doses and respond with definite gonadal atrophy, inhibition of body growth, etc. The fowl proved comparatively resistant, however, and hence it was decided to perform a second experiment on a higher dose level. For this purpose twelve 2-day-old single-combed white Leghorn chicks weighing 30–35 gm. were given 1 mg. of estradiol in 0.1 cc. of peanut oil subcutaneously twice daily for a period of 95 days. Twelve similar birds served as untreated controls. The experiment is not quite comparable with that summarized in the table, because the amount of estradiol given was still inferior to the dose level at which the other steroids were administered during the latter half of the previous experiment. However, folliculoids are so toxic that even the 2 mg./day which we gave caused marked stunting of growth and six deaths among our birds during the course of the first 10 days. After this a certain degree of adaptation occurred, since the animals resumed their growth and, though somewhat subnormal in size, appeared to be quite healthy. In order to save space the organ weights of this complementary experiment will not be tabulated. Suffice it to mention the most striking changes. The uropygial glands and the bursae of Fabricius showed practically complete involution in the animals which succumbed during the first fortnight, but in those killed on the ninety-fifth day of the experiment the bursae began to recover and the uropygial glands were actually above normal in size. This result confirms our above-mentioned observations concerning adaptation to methyltestosterone, D.C.A. and androstenedione, as it is readily noticeable from the table that between the forty-fifth and the ninety-fifth day of the experiment the weight loss of the uropygial glands was completely restored, while the bursa

still continued to lose weight although occasional lymphatic islets reappeared in its stroma. In spite of such prolonged treatment with these high doses of estradiol we found, in confirmation of Emmens ('39), that in the fowl neither the adrenals nor the pituitaries show any enlargement comparable to that obtained under similar conditions in mammals. Since our previous experiments have shown that very young rats are equally insensitive to the adrenal and pituitary enlarging effect of folliculoids (Selye and Albert, '42b), it is possible that this insensitivity is a common feature of comparatively early stages both in the ontogenetic and in the phylogenetic scale of development. It will be remembered that the lower vertebrates (amphibia, reptiles) resemble young mammals in their ability to grow after hypophysectomy. This is another observation which appears to support the concept according to which ontogenetic maturation reproduces the gradual acquisition of hormone sensitivity characteristic of phylogenetic development. In this second estradiol experiment generalized adiposity — comparable to that observed by Zondek ('41) — was again not detectable.

SUMMARY

A morphological investigation of the changes induced in the fowl by chronic overdosage with a number of steroid compounds revealed the following facts. Desoxycorticosterone acetate (D.C.A.) causes nephrosclerosis with cardiovascular changes similar to those seen in Bright's disease. In the acute stages this condition is accompanied by marked tissue edema and water accumulation in the serous cavities of the body. The gonads show especially pronounced changes during this acute stage. The testes are enlarged in an elephanthiasis-like manner, owing to the accumulation of enormous amounts of fluid in the lumina of the spermatogenic tubules. The ovaries show stroma edema and occasionally cystic dilatation of the follicles. In the chronic stages of D.C.A. overdosage generalized adiposity was prominent in both sexes.

The adrenals exhibited compensatory cortical atrophy following prolonged overdosage with D.C.A., and to a lesser degree, also, after prolonged treatment with progesterone, acetoxy-pregnenolone and methyl-testosterone. Estradiol failed to elicit the adrenal cortical hypertrophy which it is known to produce in mammals, and it also failed to enlarge the hypophysis.

The Leydig cells of the testes underwent involution following prolonged overdosage with all hormonally active steroids studied in this investigation. This involution tended to inhibit the normal development of the comb, except in the case of compounds whose inherent testoid potency compensated for the inhibition of testis hormone secretion.

The uropygial gland and the bursa of Fabricius are both under the influence of steroid hormones. The morphological development of these typical avian organs is most actively inhibited by large doses of folliculoids and testoids. However, following long continued treatment with these compounds some measure of tolerance is acquired and the above-mentioned organs tend to regain their normal size in spite of continued treatment.

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PLATE 1

EXPLANATION OF FIGURES

1 Organs of a normal pullet whose body weight and age were the same as those of the bird shown in figure 2.

2 Pullet killed after 45 days of D.C.A. treatment. Note enlargement of kidney, heart and liver and beginning adrenal involution. The surface of the kidney is extremely irregular. The pericardium is filled with fluid and excessive amounts of adipose tissue are visible around the heart, the large blood vessels and the kidney.

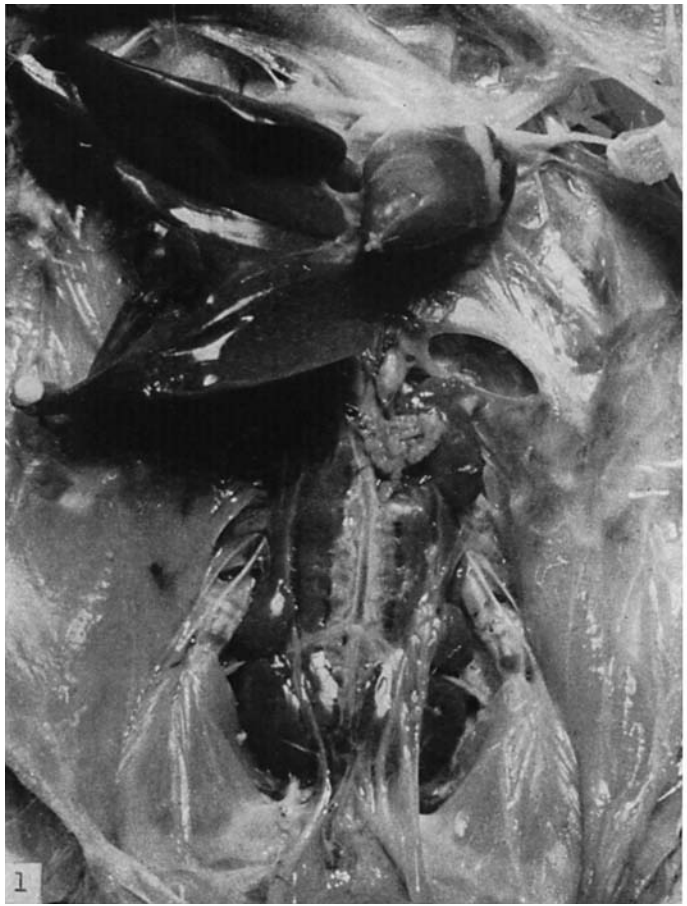
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PLATE 2

EXPLANATION OF FIGURES

3 Section through normal kidney showing medium sized artery and vein in a fowl whose age and weight were the same as those of that whose kidney is shown in figure 4.

4 Kidney of chick treated with D.C.A. for 95 days showing cross section through a vein of approximately the same size as that represented in figure 3. It will be noted that the walls of this vein are slightly thickened while that of the accompanying artery are enormously enlarged in comparison with the vessels of figure 3. The adventia of the artery shows some edema and signs of degeneration.

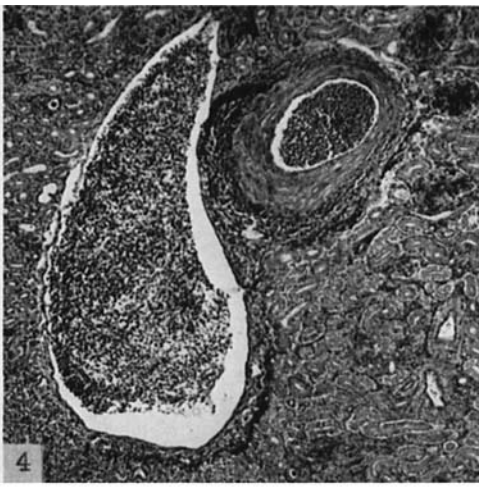
5 Section through the renal cortex of a chick of the same size and age as the birds whose kidneys are reproduced in figures 6, 7 and 8. The magnification is also the same as that of the following three pictures.

6 Intense glomerular enlargement and sclerosis in the kidney of a chick treated with D.C.A. for 95 days.

7 Treatment as in figure 6 but in this case formation of hyaline casts in the tubules and leukocytic infiltration of the stroma are especially obvious. ''Epithelial crescents'' are clearly visible in the two renal corpuscles of this field.

8 Three enlarged sclerotic renal corpuscles in the kidney of a bird after 95 days of progesterone treatment.


3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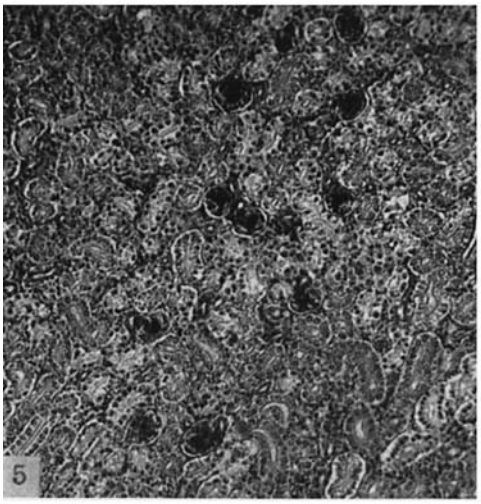
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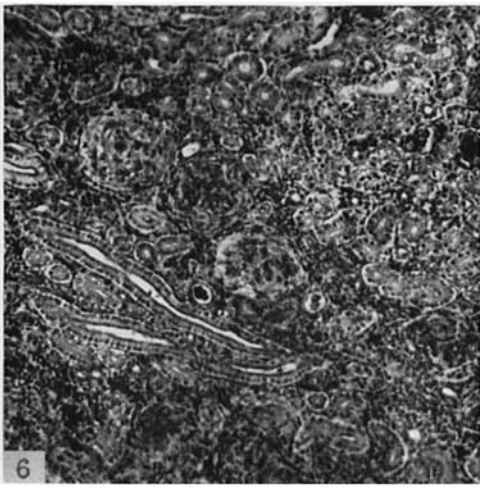
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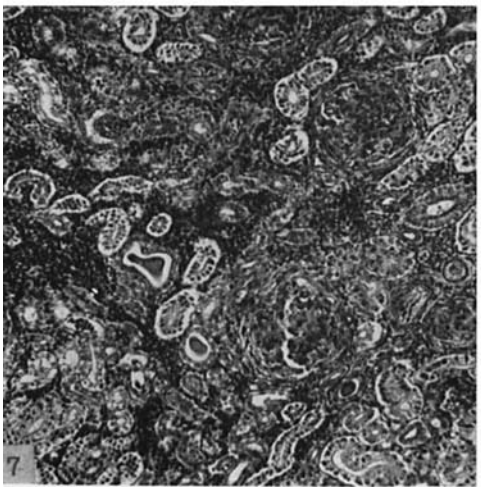
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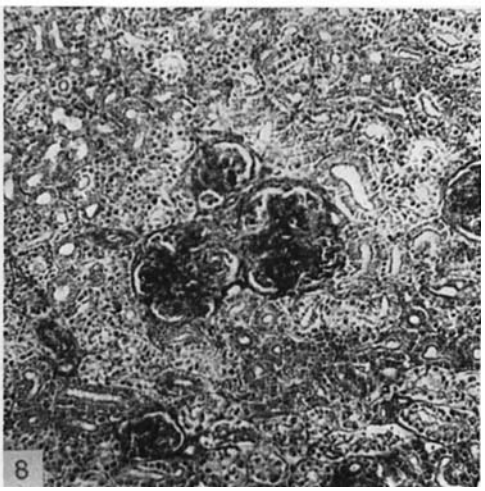
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PLATE 3

EXPLANATION OF FIGURES

9 Enlarged kidney and enormously distended testes of a chick (left) following 20 days of D.C.A. treatment in comparison with the normal organs of an untreated control of the same age (right).

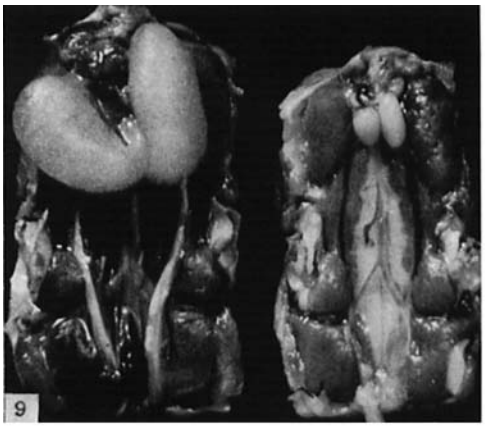
10 Enlarged kidneys and cystically distended ovary of a chick (left) following 20 days of D.C.A. treatment in comparison with the normal organs of an untreated control of the same age (right). Note that during this early edematous stage the renal surface is still smooth.

11 Section through normal testis of a chick of the same age and size as that whose testis is shown in figure 12.

12 Greatly distended seminiferous tubules in the testis of a chick treated with D.C.A. for 20 days. Note the flat epithelium lining the tubules and the absence of any spermatogenic activity. Same magnification as figure 11.

13 Bursa of Fabricius in normal chick of the same age and size as that whose bursa is shown in figure 14. Note epithelial lining of crypts and well developed lymphatic tissue with light germinal centers.

14 Bursa of Fabricius of a chick which received methyl-testosterone for 45 days. Note complete disappearance of lymphatic stroma. The organ now consists merely of the lining epithelium and a small amount of connective tissue stroma. Same magnification as figure 13.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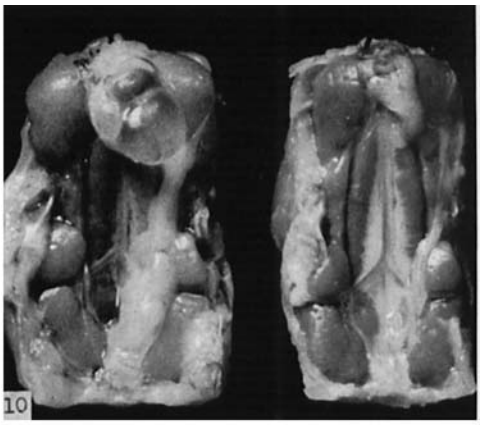
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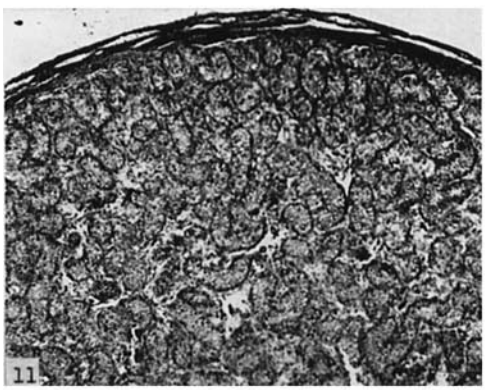
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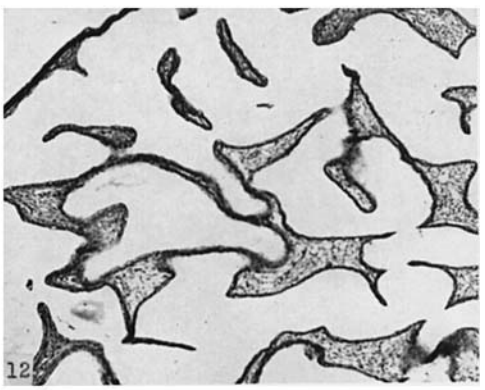
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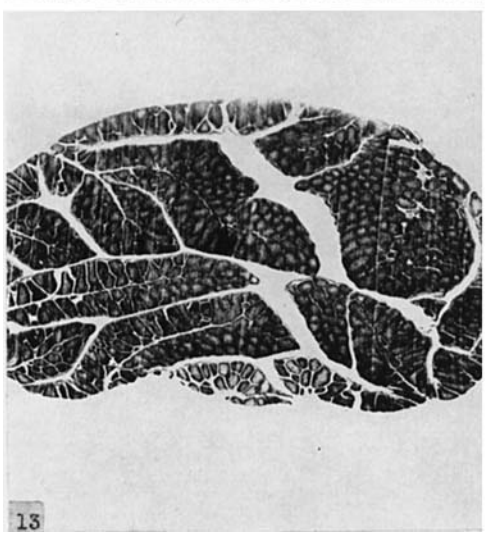
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